UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,308	10/24/2001	M. Parameswara Reddy	2058-181	8198

22471 7590 09/11/2007

PATENT LEGAL DEPARTMENT/A-42-C
BECKMAN COULTER, INC.
4300 N. HARBOR BOULEVARD
BOX 3100
FULLERTON, CA 92834-3100

EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

MAIL DATE	DELIVERY MODE
09/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/033,308	REDDY ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-12,18,25,29,32-34 and 38-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-12,18,25,29,32-34,38 and 42* is/are rejected.

7)☒ Claim(s) *39-41* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/8/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed July 5, 2007 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

3. Please note that the following action has been made non-final in view of the fact that not all of the following rejections were necessitated by Applicants' amendments.

Status of the Claims

4. Claims 1, 5-12, 18, 25, 29, 32-34, and 38 were pending. Applicants amended claims 1 and 12. In addition, Applicants added claims 39-42. Therefore, claims 1, 5-12, 18, 25, 29, 32-34, and 38-42 are pending and examined on the merits.

Withdrawn Objections/Rejections

5. The objection to claim 12 is withdrawn in view of Applicants' amendments thereto. The 35 U.S.C. § 112, first paragraph rejection is withdrawn in view of Applicants' amendments to claims 1 and 12. The Swenson et al. rejection under 35 U.S.C. § 103(a) has been withdrawn in favor of the newly revised rejection noted below.

New Rejections

Objections to the Claims

6. Claim 33 is objected to because of the following informalities:

A. Claim 33 contains the misspelled word "polyproplyene" in line 3. Correction is requested.

Claims Rejections - 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 39 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention. This is a new matter rejection.

A. Claim 39 was added in the 7/5/07 Response. However, support cannot be found for the word "metabolite" in association with "any" drug of abuse. The specification only discusses "metabolism" with respect to cocaine, morphine and nicotine (e.g., see paragraph 21). If applicant believes this rejection is in error, applicant must disclose where in the specification support for this amendment can be found in accordance with MPEP §§ 2163.06 and 714.02. Therefore, claim 39 and all dependent claims are rejected for containing new matter.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all

obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 29 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Swenson et al. (Swenson et. al. "Novel Substitutions of Position 6 of LHRH Antagonist to Improve Potency and Safety" *Peptides: Chemistry, Structure and Biology* **1996**, *273*, 653-654) in view Stolowitz et al. (WO 87/06586) (Date of Publication is **November 5, 1987**) (of record) and Gasson et al. (WO 92/04353) (Date of Patent is **March 19, 1992**) and Eichler et al. (Eichler et al., "Evaluation of Cotton as a Carrier for Solid-Phase Synthesis" Peptide Research **1991**, *4(5)*, 296-307) and Beyerman et al. (Beyerman et al., "Use of Carbonylditriazole in Peptide Synthesis" Recueil **1961**, 80, 1372-1375) and Englebretsen et al. (Englebretsen et al., "Solid phase peptide synthesis on hydrophilic supports. Part II – Studies using Perloza beaded cellulose" *Int. J. Peptide Protein Res.* **1992**, *40*, 487-496) and Elsner et al. (WO 94/03530) (Date of Patent is **February 17, 1994**) as evidenced by Tripathi (e.g., Tripathi et al. Nucleic Acids Research **2004**,

33(13), 4345-4356) and Gehlsen (U.S. Patent Applic. No. US 2003/0091553 A1) (Publication Date is **May 15, 2003**).

For ***claim 29***, Swenson et al. (see entire document) teach a method of attaching a biological molecule to a solid support (e.g., see page 653, paragraphs 1 and 2 wherein an LHRH agonist decapeptide is attached to an MBHA resin). In addition, Swenson et al. disclose **(a)** providing a solid support having at least one available amino group the solid support being formed from a material selected from the group consisting of cellulose agarose polypropylene polystyrene polymethacrylate nylon (e.g., see page 653, paragraph 2 wherein MBHA is disclosed and the free amino group is the Fmoc deprotected BocDLys(N-ε-Fmoc) at position six). Swenson et al. do not actually state that this resin is a polystyrene resin but the Examiner contends that this is an inherent property of the molecule or, alternatively, would be immediately envisioned as exemplified by Tripathi (e.g., see page 4347, column 1, first full paragraph defining MBHA resin as "polystyrene beads carrying [i.e., modified with] 4-mthyl benzhydrylamine" and/or modified with a peptide containing a deprotected BocDLys(N-ε-Fmoc) at position 6). Swenson et al. also disclose **(b)** reacting the available amino group on the solid support with an activating compound to form an activated support (e.g., see Swenson et al., page 653, paragraph 2, wherein 1,1'-carbonyldiimide is disclosed). Swenson et al. also disclose **(c)** providing a biological molecule wherein the biological molecule is selected from the group consisting of hormones therapeutic drugs and drugs of abuse (e.g., see Table 1 wherein compound 11 containing "histamine" would qualify as a hormone and/or therapeutic drug). Swenson et al. do not explicitly state that histamine is a hormone and/or therapeutic drug

but the Examiner contends that this is an inherent property of the molecule as evidenced by Gehlsen (e.g., see Gehlsen, abstract and description; see especially claim 5, wherein "histamine" is used for inhibiting and reducing reactive oxygen species (ROS)-mediated oxidative damage to hepatic cells). Finally, Swenson et al. also disclose **(d)** reacting the biological molecule with the activated support thereby covalently attaching the biological molecule to the solid support so that the biological molecule is available for use in an assay (e.g., see page 653, paragraph 2, "After removal of the Fmoc group the peptide-resin was treated first with 1,1'-carbonyldiimide [i.e., to form the activated resin] and then with the appropriate amine [i.e., the compounds listed in Table 1]"), which forms the requisite "urea" linkage.

The prior art teachings of Swenson et al. differ from the claimed invention as follows:

For ***claim 29***, Swenson et al. fail to teach an activating compound such as 1,2,4-carbonyl di-triazole. Swenson et al. only teach 1,1'-carbonyldiimide.

For ***claim 42***, Swenson et al. fail to teach supports selected from the group consisting of cellulose, agarose, polypropylene, polymethacrylate, and nylon.

However, the combined references of Stolowitz et al., Englebretsen et al., Gasson et al., Beyerman et al., Eichler et al., and Elsner et al. teach the following limitations that are deficient in Swenson et al.:

For ***claim 29***, Stolowitz et al. disclose, for example, 1,2,4-carbonyl di-triazole as a coupling agent (e.g., see Stolowitz et al., page 10, paragraph 1, "A variety of azolides other than N,N'-carbonyl-dimidazole [i.e., also known as 1,1'-diimdiazole as recited

above in Swenson]... may be employed ... N,N'-carbonyldi-1,2,4-triazole"; see also Stolowitz et al., abstract; see also page 9, formula 7 wherein the urea linkage is shown; see also Summary of Invention, "In addition, a number of important specific objectives are also achieved using the present invention, including: The use of N,N'-carbonyldiimidazole for the activation of a chromatographic support with other than pendant hydroxyl groups; The preparation of a urea derivative of a bonded phase chromatographic support and the unique hydrophilic nature of the urea linkage"; see also Example 1, lines 8-18; see also page 3, lines 14-20; see also page 3, lines 21-26). Likewise, Gasson et al. also disclose carbonyl di-triazoles as standard coupling reagents that are "equivalent" to the carbonyldiimides disclosed in Swenson et al. (e.g., see Beecham et al., page 20, lines 25-35, "Other reactive N-acylating derivatives [that can be used include] ... a condensing agent such as a carbonyldiimide ... a suitable carbonyl compound, for example, N,N'-carbonyldiimidazole or N,N'-carbonylditriazole"

For ***claim 42***, Eichler disclose, for example, the use of supports selected from the group consisting of cellulose, agarose, polypropylene, polymethacrylate, and nylon for peptide synthesis. For example, Eichler et al. the use of polypropyelene (e.g., see Eichler et al., page 296, column 3, paragraph 3; see also last paragraph in same column; see also table 4 comparing polypropylene to cotton and paper; see also page 299, column 1, last paragraph, "Comparative Synthesis on Polystyrene Resin and Planar Carriers" section; see also page 399, column 3, paragraph 2), polyethylene (e.g., see Eichler et al., page 296, column 3, paragraph 3; see also page 306, column 1, paragraph 1), polystyrene (e.g., see Eichler et al., page 299, column 1, last paragraph, "Comparative Synthesis on

Polystyrene Resin and Planar Carriers" section; see also Table 9 comparing cotton to polystyrene; see also page 302, column 2), polyamide (e.g., see Eichler et al., page 302, column 2; see also page 303, column 1, first paragraph), and cotton i.e., cellulose (e.g., see Eichler et al., title and abstract; see also comparative tables) as supports in solid-phase synthesis. Likewise, Englebretsen et al. disclose the use of a wide variety of solid supports including cellulose, polystryrene, etc . (e.g., see Englebretsen et al., abstract and results). In addition, Elsner et al. also disclose the use of a wide variety of solid supports and/or reagents (e.g., see Elsner et al., abstract wherein activated polysaccharides like agarose are disclosed; see also Detailed Description of the Invention and Examples).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the 1,2,4-carbonyl di-triazole coupling agent as disclosed by the combined teachings of Stolowitz et al., Englebretsen et al., Gasson et al., Beyerman et al., Eichler et al., and Elsner et al. to couple the compounds listed in Table 1 of Swenson et al. the immobilized peptide because all of these reagents are art recognized coupling agents (e.g., see Gasson, page 20, last paragraph; see also Stolowitz et al., page 10, paragraph 1, "A variety of azolides other than N,N'-carbonyl-diimidazole [i.e., the coupling agent used by Swenson] may be employed ... include[ing] N,N'-carbonyldipyrazole, N,N'-carbonyldi-1,2,3-triazole, N,N'-carbonyldi-1,2,4-triazole, N,N'-carbonyldiindole, N,N,-carbonylidibenzimidazole and N,N'-carbonyldibenztriazole and others."). Furthermore, a person of ordinary skill in the art would have been motivated to use the triazole because Stolowitz et al., for example, state that they obtain "near quantitative derivatization of bonded supports ... by this synthetic route" (e.g., see

Stolowitz et al., page 4, lines 29-30) and that their method is "versatile" because "almost [an] infinite variety of ligands ... can be employed as functionalizing reagents" (e.g., see Stolowitz et al., page 4, lines 34-35; see also Stolowitz et al., page 4, lines 23-25). In addition, Stolowitz et al. state that their coupling agents can be used to form "urea" linkages (e.g., see Stolowitz et al., page, 7, first full paragraph), which is exactly the same type of linkage that is being formed in Swenson et al. (e.g., see Swenson et al., page 653, paragraph 2, "we developed a method for making ureas"). Furthermore, Beyerman et al. state that "less racemization" will take place with N,N'-carbonyldi-1,2,4-triazole (e.g., see Beyerman et al., abstract). Finally, a person of skill in the art would have reasonably expected to be successful because Stolowitz et al., for example, shows the use of 1,2,4-carbonyl di-triazole in a coupling reaction involving amino groups to form ureas (e.g., see abstract; see also Summary of Invention; see also Examples). In addition, Stolowitz et al. also state, "almost [an] infinite variety of ligands ... can be employed as functionalizing reagents" (e.g., see Stolowitz et al., page 4, lines 34-35).

Alternatively, the Examiner contends that the combined references of Stolowitz et al., Englebretsen et al., Eichler et al., Beyerman et al., and Gannon stand for the proposition that a carbonyldiimide and 1,2,4-carbonyl di-triazole represent "equivalent" coupling reagents (e.g., see Gannon, page 20, last paragraph; see also see also Beyerman et al., entire document comparing various five-membered unsaturated rings including CDT and CDI as potential reagents for peptide synthesis) and, as a result, "teaching, suggestion, or motivation" to substitute one for another need not be provided. See *in In re Fout*, 675 F.2d 297, 301, 213 USPQ 532, 536 (CCPA 1982) ("Express suggestion to

substitute one equivalent for another need not be present to render such substitution obvious"). See also *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __, 2007 WL 1237837, at *12 (2007). That is, it would be obvious to make a simple substitution like 1,2,4-carbonyl di-triazole for 1,1'-carbonyldiimide. because it was known at the time of filing that the both could be used as coupling agents (e.g., see above). Furthermore, this substitution would have led to predictable because it was known that a urea linkage would be produced in either case (see above).

In addition, it would have been prima *facie obvious* to use any of the claimed solid supports for solid-phase synthesis and/or immobilization because all of the materials were routinely used for this purpose (e.g., see Eichler et al., abstract and results showing usefulness of various materials for peptide synthesis. Thus, it would have been prima facie obvious to substitute one material for another because the results are predictable i.e., solid phase synthesis would occur on any of these materials with favorable results (e.g., see comparisons sections and corresponding tables). See also *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __, 2007 WL 1237837, at *12 (2007). Furthermore, a person of skill in the art would have been motivated to use any of these materials because they allow for high yields with facile work up procedures. In addition, a person of skill in the art would reasonably have expected to be successful because all of these materials had been routinely used for solid phase synthesis using activating agents including CDI, CDT, etc.

Response

11. To the extent that Applicants' previous arguments could be applied to the newly cited rejection above, the following points are noted:

[1] Applicants argue, "Swenson et al. does not disclose step (b) of the claimed method" (e.g., see 7/5/07 Response, page 7, last paragraph).

[1] In response to applicant's arguments against the Swenson et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the combined references teach step (b) as noted in the above rejection.

[2] Applicants argue, "Since the MBHA resin is linked to the peptide via an amide bond during SPPS, the amino group on the MBHA resin is no longer available for activation" (e.g., see 7/5/07 Response, page 8, first full paragraph).

[2] The Examiner respectfully disagrees and has clarified the above rejection to more adequately address this point. Specifically, the MBHA resin contains a free amine with the BocDLys(N-ε-Fmoc) is deprotected (i.e., the amino protecting F-moc groups is removed) to reveal a free amine for further amino acid coupling (e.g., see page 643, paragraph 2). Thus, Swenson et al. disclose an available amino group on the solid support.

[3] Applicants argue, "Swenson et al. does not fairly suggest providing a hormone or therapeutic drug consisting of histamine" and cite In re Wesslau in support of this position suggesting that histamine is not inherently "therapeutic" in this context (e.g., see 7/5/07

Response, bottom of page 8)

[3] "From the standpoint of patent law, a compound and all its properties are inseparable." *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963). Gehlsen expressly states that "histamine" can be used as a therapeutic drug for inhibiting and reducing reactive oxygen species (ROS)-mediated oxidative damage to hepatic cells (e.g., see Gehlsen, abstract and description; see especially claim 5). Thus, it is clear that a therapeutic drug has been reacted with the activated resin regardless of whether Swenson et al. recognized it as such.

[4] Applicants argue, "Swenson et al. does not disclose step (d) of the claimed method ... subsequent treatment with the 'appropriate amine' covalently attaches substituents to the peptide, not the solid support" (e.g., see 7/5/07 Response, paragraph bridging pages 8 and 9).

[4] As noted above, the "peptide-MBHA" can be considered as the "solid support" (see newly amended rejection above), which is then reacted after deprotection of the Fmoc group with the list of amines in table 1 including the therapeutic histamine reagent.

[5] Applicants argue, "Swenson et al. does not disclose 1,2,4-carbonyl di-triazole and neither Stolowitz et al. nor Gasson teach the equivalence of carbonyldiimide and 1,2,4-carbonyl di-triazole as coupling agents ... Gasson, page 20, last paragraph, merely lists a number of condensing agents ... Picking and choosing a specific compound used for an entirely different purpose in the cited reference indicates the impermissible use of hindsight to show obviousness ... [and further note] nowhere in the exhaustive laundry list of compounds [disclosed by Stolowitz et al. and Gasson] is found the 1,1'-carbonyldiimide disclosed by Swenson et al.

Accordingly ... the proposition that a carbonyldiimide and 1,2,4-carbonyl di-triazole represent 'equivalent' coupling reagents" lacks support in the cited references" (e.g., see 7/5/07 Response, bottom of page 9).

[5] In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Here, both Stolowitz et al. and Gasson teach that a wide variety of structurally related compounds can be used as coupling agents including carbonyl-diimidazoles (e.g., see Stolowitz et al., page 10, lines 1-2) and carbonyl-ditriazoles (e.g., see Stolowitz et al., page 10, lines 4 and 5). Thus, a person of ordinary skill would know based on the teachings of these two references that a wide range of both carobonyl-diimidazoles and carbonyldi-triazoles could be used to effectuate the claimed coupling reaction.

In addition, it should be noted that N,N'-carbonyl-dimidazole recited in Stolowitz is the same compound as the 1,1'-carbonyl-dimidazole recited in Swenson and thus Applicants argument that "nowhere in the exhaustive laundry list of compounds is found the 1,1'-carbonyldiimide disclosed by Swenson et al. is without merit.

[6] Applicants argue, "the combined teachings of Stolowitz et al. and Gasson fail to cure the deficiencies of Swenson et al." (e.g., see 7/5/07 Response, page 10, paragraph 1).

[6] There are no deficiencies in the Swenson et al. for the reasons outlined in [1]-[5] above and, as a result, Applicants' arguments are moot.

[7] Applicants argue, "there must be something in the prior art to suggest not only the desirability of combining the references, but a suggestion that they be combined in the particular manner and configuration as the claimed invention ... [which] has not [been] identified" (e.g., see 7/5/07 Response, page 10, paragraph 2).

[7] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, a person of skill in the art would have been motivated to use the triazole because Stolowitz et al., for example, state that they obtain "near quantitative derivatization of bonded supports ... by this synthetic route" (e.g., see Stolowitz et al., page 4, lines 29-30) and that their method is "versatile" because "almost [an] infinite variety of ligands ... can be employed as functionalizing reagents" (e.g., see Stolowitz et al., page 4, lines 34-35; see also Stolowitz et al., page 4, lines 23-25). In addition, Stolowitz et al. state that their coupling agents can be used to form "urea" linkages (e.g., see Stolowitz et al., page, 7, first full paragraph), which is exactly the same type of linkage that is being formed in Swenson et al. (e.g., see Swenson et al., page 653, paragraph 2, "we developed a method for making ureas").

Alternatively, the Examiner contends that the combined references of Stolowitz et al. and Gannon stand for the proposition that a carbonyldiimide and 1,2,4-carbonyl di-triazole represent "equivalent" coupling reagents (e.g., see Gannon, page 20, last paragraph) and, as a result, "teaching, suggestion, or motivation" to substitute one for another need not be provided. See *in In re Fout*, 675 F.2d 297, 301, 213 USPQ 532, 536 (CCPA 1982) ("Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious"). See also *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __, 2007 WL 1237837, at *12 (2007). That is, it would be obvious to make a simple substitution like 1,2,4-carbonyl di-triazole for 1,1'-carbonyldiimide. because it was known at the time of filing that the both could be used as coupling agents (e.g., see above). Furthermore, this substitution would have led to predictable because it was known that a urea linkage would be produced in either case (see above).

12. Claims 1, 5-12, 18, 25, 32-34, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sompuram et al. (U.S. Patent No. 7,011,940 B1) (filed April 14, 2000) in view of Stolowitz et al. (WO 87/06586) (Date of Publication is **November 5, 1987**) (of record) and Gasson et al. (WO 92/04353) (Date of Patent is **March 19, 1992**) and Goldstein et al. (Goldstein et al., "Chemically Modified Nylons as Supports for Enzyme Immobilization" *Biochem. J.* **1974**, *143*, 497-509) and Eichler et al. (Eichler et al., "Evaluation of Cotton as a Carrier for Solid-Phase Synthesis" Peptide Research **1991**, *4(5)*, 296-307) and Beyerman et al. (Beyerman et al., "Use of Carbonylditriazole in Peptide Synthesis" Recueil **1961**, 80, 1372-1375) and Englebretsen et al. (Englebretsen et al., "Solid phase peptide synthesis on hydrophilic supports. Part II – Studies using Perloza beaded cellulose" *Int. J. Peptide Protein Res.* **1992**, *40*, 487-496) and Elsner et al.

(WO 94/03530) (Date of Patent is **February 17, 1994**) and Andersson et al. (Andersson et al., "Macroporous polymethacrylate: a new support for continuous-flow solid phase peptide synthesis" Pept. 1992, Proc. Eur. Pept. Symp., 22nd (1993), Meeding date **1992**, 265-266).

For ***claim 1***, Sompuram et al. disclose a method of attaching a biological molecule to a solid support comprising **(a)** providing a solid support having at least one available amino group (e.g., see figure 13 showing free amino group). In addition, Sompuram et al. disclose that the solid support is formed from a material selected from the group consisting of cellulose, agarose, polypropylene, polystyrene, polymethacrylate, and nylon (e.g., see column 10, first full paragraph, "The matrix can be manufactured of materials capable of binding macromolecules ... [including] nylon ... [which is] derivatized by the manufacturer so that there is an abundance of free carboxyl groups on their surface. This allows for the coupling of macromolecules to the carboxyl group through an amine"). In addition, Sompuram et al. disclose **(b)** reacting the available amino group on the solid support with an activating compound to form an activated support (e.g., see figure 13 showing activation; see also column 10, paragraph 1 noted above). In addition, Sompuram et al. disclose **(c)** providing a biological molecule having at least one reactive amino thiol or hydroxyl group wherein the biological molecule is selected from the group consisting of nucleic acids, polypeptide chains, and carbohydrates (e.g., see figure 11 showing formation of a urea linkage via the "free" amino group of a protein or DNA; see also column 4, paragraphs 1 and 2; see also column 6, paragraph 1; see also column 18, line 13; see also examples; see also claim 21). Finally, Sompuram et al. also disclose **(d)** reacting the biological molecule with the

activated support thereby covalently attaching the biological molecule to the solid support so that the biological molecule is available for use in an assay (e.g., see figures 11 and 13).

For ***claim*** 5, Sompuram et al. disclose a method according to claim 1 wherein step **(c)** comprises depositing between about 5 to about 25 nanoliters of the biological molecule in a circular spot at one or more sites on the activated support wherein the circular spot has a diameter of between about 10 microns to about 500 microns at one or more sites on the activated support (e.g., see figures 2 and 3; see also column 4, second to last paragraph; see also column 20, paragraphs 3 and 4; see also column 20, last paragraph; see also column 9, last two paragraphs). In addition, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955). Consequently, any small changes between the size of the spots and the amount of material applied would not be inventive absent some showing of criticality or unexpected results.

For ***claim 6***, Sompuram et al. disclose a method according to claim 5 wherein one or both of the activating compound and the biological molecule is printed onto the solid support (e.g., see figures 2 and 3).

For ***claim 7***, Sompuram et al. disclose a method according to claim 1 wherein in one or both of step (b) and step (d) occurs in a humid chamber (e.g., see column 5, line 34).

For ***claim 8***, Sompuram et al. disclose a method according to claim 6 wherein in

one or both of step (b) and step (d) occurs in a humid chamber (e.g., see column 5, line 34).

For ***claim 9 and 11***, Sompuram et al. disclose a method according to claim 1 wherein step (b) occurs in an organic solution (e.g., see figure 13; see also column 26, lines 30-35 wherein various solvents are disclosed). Please note that the choice of solvent for a reaction is considered routine within the art absent some unexpected results.

For ***claim 12***, Sompuram et al. disclose in addition to the limitations set forth above the use of a plate (e.g., see figure 13).

For ***claim 25***, Sompuram et al. disclose a method according to claim 1 wherein the biological molecule is an oligonucleotide having at least one free amino or thiol group (e.g., see figure 11 showing binding via free amino group).

For ***claim 32***, Sompuram et al. teach the use of a plate or film (e.g., see figure 13).

For ***claim 33***, Sompuram et al. disclose a method according to claim 1 wherein the solid support is an amine derivatized organic polymer selected from the group consisting of polypropylene, polystyrene, polymethacrylate, and nylon (e.g., see column 10, lines 9-14 wherein nylon is disclosed).

For ***claim 34***, Sompuram et al. disclose a method according to claim 1 wherein the biological molecule is an amino derivatized oligonucleotide (e.g. see figure 11).

For ***claim 38***, Sompuram et al. disclose in addition to the limitations set forth above for independent claims 1 and 12 the use of an amine-derivatized oligonucleotide (e.g., see figure 11).

The prior art teachings of Sompuram et al. differ from the claimed invention as

follows:

For ***claim 1***, Sompuram et al. fail to teach an activating compound such as 1,2,4-carbonyl di-triazole. Swenson et al. only teach N,N'-carbonyldiimide. In addition, Sompuram et al. fail to teach that nylon can be derivatized with free amino groups. Sompuram et al. only disclose the derivatization of nylon with carboxylic acids for purposes of functionalizing the nylon for coupling reactions (e.g., see above).

For ***claim 10***, Sompuram et al. fail to disclose a method according to claim 9 wherein step (b) occurs in the presence of a tertiary organic base.

For ***claim 18***, Sompuram et al. fail to disclose a method according to claim 1 further comprising the step of washing from the solid support non-bound compounds after step (b) and before step (c).

However, the combined references of Stolowitz et al., Andersson et al., Elsner et al., Englebretsen et al., Gasson et al., Beyerman et al., Eichler et al., and Goldstein et al. teach the following limitations that are deficient in Sompuram et al.:

For ***claim 1***, Stolowitz et al. disclose, for example, 1,2,4-carbonyl di-triazole as a coupling agent (e.g., see Stolowitz et al., page 10, paragraph 1, "A variety of azolides other than N,N'-carbonyl-diimidazole ... may be employed ... [including] ... N,N'-carbonyldi-1,2,4-triazole"; see also Stolowitz et al., abstract; see also page 9, formula 7 wherein the urea linkage is shown; see also Summary of Invention, "In addition, a number of important specific objectives are also achieved using the present invention, including: The use of N,N'-carbonyldiimidazole for the activation of a chromatographic support with other than pendant hydroxyl groups; The preparation of a urea derivative of

a bonded phase chromatographic support and the unique hydrophilic nature of the urea linkage"; see also Example 1, lines 8-18; see also page 3, lines 14-20; see also page 3, lines 21-26). Likewise, Gasson et al. also disclose carbonyl di-triazoles as standard coupling reagents that are "equivalent" to the carbonyldiimides disclosed in Sompuram et al. (e.g., see Beecham et al., page 20, lines 25-35, "Other reactive N-acylating derivatives [that can be used include] ... a condensing agent such as a carbonyldiimide ... a suitable carbonyl compound, for example, N,N'-carbonyldiimidazole or N,N'-carbonylditriazole"). In addition, Goldstein et al. teach nylon, like the nylon disclosed in Sompuram et al. can be functionalized with a wide variety of groups including amino groups for the purpose of immobilizing proteins such as enzymes (e.g., see Goldstein et al., page 143, paragraphs 1 and 2; see also scheme 4 showing amino functionalized polyacrylamide; see also scheme 5 showing immobilization of proteins to nylon).

For ***claims 9-12***, the combined references of Stolowitz et al., Andersson et al., Elsner et al., Englebretsen et al., Gasson et al., Beyerman et al., Eichler et al., and Goldstein et al. disclose a method according to claim 9 wherein step (b) occurs in the presence of a tertiary organic base (e.g., see Stolowitz et al., Example I wherein triethylamine is used; see also Examples II-IV). The combined references also teach a wide variety of solvents and/or reagents useful in peptide synthesis (e.g., see Englebretsen et al., Materials and Methods section; see also Elsner et al., Examples).

For ***claim 18***, the combined references of Stolowitz et al., Andersson et al., Elsner et al., Englebretsen et al., Gasson et al., Beyerman et al., Eichler et al., and Goldstein et al. disclose a method according to claim 1 further comprising the step of washing from

the solid support non-bound compounds after step (b) and before step (c) (e.g., see Example 1, especially page 11, line 15).

For ***claim 33***, the combined references of Stolowitz et al., Andersson et al., Elsner et al., Englebretsen et al., Gasson et al., Beyerman et al., Eichler et al., and Goldstein et al. disclose in addition to the solid supports noted above the use of polypropylene (e.g., see Eichler et al., page 296, column 3, paragraph 3; see also last paragraph in same column; see also table 4 comparing polypropylene to cotton and paper; see also page 299, column 1, last paragraph, "Comparative Synthesis on Polystyrene Resin and Planar Carriers" section; see also page 399, column 3, paragraph 2), polyethylene (e.g., see Eichler et al., page 296, column 3, paragraph 3; see also page 306, column 1, paragraph 1), polystyrene (e.g., see Eichler et al., page 299, column 1, last paragraph, "Comparative Synthesis on Polystyrene Resin and Planar Carriers" section; see also Table 9 comparing cotton to polystyrene; see also page 302, column 2), polyamide (e.g., see Eichler et al., page 302, column 2; see also page 303, column 1, first paragraph), and cotton i.e., cellulose (e.g., see Eichler et al., title and abstract; see also comparative tables) as supports in solid-phase synthesis. Likewise, Elsner et al. also teach a wide variety of solid supports and reagents for solid phase synthesis including, for example, agarose (e.g., see Elsner et al., abstract; see also Detailed Description; see also Examples). In addition, Andersson et al. teach the use of polymethacrylate for solid-phase peptide synthesis (e.g., see Andersson et al., title).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the 1,2,4-carbonyl di-triazole coupling agent as

disclosed by the combined teachings of Stolowitz et al., Goldstein et al., Eichler et al., and Gasson et al. for the N,N'-carbonyldiimidazole as disclosed by Sompuram et al. (e.g., see Sompuram et al., figure 13) to immobilize peptides, nucleic acids etc. because all of these reagents represent art recognized coupling agents (e.g., see Gasson, page 20, last paragraph; see also Stolowitz et al., page 10, paragraph 1, "A variety of azolides other than N,N'-carbonyl-diimidazole [i.e., the coupling agent used by Sompuram] may be employed ... include[ing] N,N'-carbonyldipyrazole, N,N'-carbonyldi-1,2,3-triazole, N,N'-carbonyldi-1,2,4-triazole, N,N'-carbonyldiindole, N,N,-carbonylidibenzimidazole and N,N'-carbonyldibenztriazole and others."). Furthermore, a person of skill in the art would have been motivated to use the triazole because Stolowitz et al., for example, state that they obtain "near quantitative derivatization of bonded supports ... by this synthetic route" (e.g., see Stolowitz et al., page 4, lines 29-30) and that their method is "versatile" because "almost [an] infinite variety of ligands ... can be employed as functionalizing reagents" (e.g., see Stolowitz et al., page 4, lines 34-35; see also Stolowitz et al., page 4, lines 23-25). In addition, Stolowitz et al. state that their coupling agents can be used to form "urea" linkages (e.g., see Stolowitz et al., page, 7, first full paragraph), which is exactly the same type of linkage that is being formed in Sompuram et al. (e.g., see Sompuram et al., figure 11). Furthermore, Beyerman et al. state that "less racemization" will take place with N,N'-carbonyldi-1,2,4-triazole and that organic solvents like DMF can be used which are more favorable for peptide synthesis (e.g., see Beyerman et al., abstract), which would encompass the peptide synthesis disclosed by Sompuram et al. Finally, a person of skill in the art would have reasonably expected to be successful

because Stolowitz et al. shows the use of 1,2,4-carbonyl di-triazole in a coupling reaction involving amino groups to form ureas (e.g., see abstract; see also Summary of Invention; see also Examples). In addition, Stolowitz et al. also state, "almost [an] infinite variety of ligands ... can be employed as functionalizing reagents" (e.g., see Stolowitz et al., page 4, lines 34-35). In addition, Goldstein et al. provide a facile method for producing nylon with the requisite "free amino groups" for protein immobilization (e.g., see Goldstein et al., page 497, paragraphs 1 and 2; see also scheme 4 showing example of nylon with free amino group).

Alternatively, the Examiner contends that the combined references of Stolowitz et al., Goldstein et al., Eichler et al., and Gasson et al. stand for the proposition that a carbonyldiimide and 1,2,4-carbonyl di-triazole represent "equivalent" coupling reagents (e.g., see Gannon, page 20, last paragraph; see also Beyerman et al., entire document comparing various five-membered unsaturated rings including CDT and CDI as potential reagents for peptide synthesis) and, as a result, "teaching, suggestion, or motivation" to substitute one for another need not be provided. See *in In re Fout*, 675 F.2d 297, 301, 213 USPQ 532, 536 (CCPA 1982) ("Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious"). See also *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __, 2007 WL 1237837, at *12 (2007). That is, it would be obvious to make a simple substitution like 1,2,4-carbonyl di-triazole for 1,1'-carbonyldiimide because it was known at the time of filing that the both could be used as coupling agents (e.g., see above). Furthermore, this substitution would have led to predictable because it was known that a urea linkage would be produced in either case

(see above).

In addition, it would have been prima *facie obvious* to use any of the claimed materials for the synthesis of peptides/nucleic acids at the time the invention was made because all of the materials were known and had been used for a long time in this regard (e.g., see Eichler et al., abstract and results showing usefulness of various materials for peptide synthesis. Thus, it would have been prima facie obvious to substitute one material for another because the results are predictable i.e., peptides could be produced on any of these materials with favorable results (e.g., see comparisons sections and corresponding tables). See also *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __, 2007 WL 1237837, at *12 (2007). Furthermore, a person of skill in the art would have been motivated to use any of these materials because they allow for high yields with facile work up procedures. In addition, a person of skill in the art would reasonably have expected to be successful because all of these materials had been routinely used in peptide synthesis, which reads on the peptide synthesis disclosed by Stolowitz.

Allowable Subject Matter

13. Claims 39-41 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The

examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
August 23, 2007

JON EPPERSON
PRIMARY EXAMINER